REMARKS

Claims 1-12 and 14-17 are pending in this application. Claims 7-9 and 18-22 have been withdrawn by the examiner. Claim 13 has been canceled without prejudice or disclaimer. Claims 1-6, 10-12 and 14-17 are currently under examination. Without acquiescing in any rejection, claim 1 is amended for clarity and as discussed herein. Support for the amendment can be found throughout the specification. For example, see at page 4, section entitled "Sample Preparation", page 5 (in particular, line 1 for reference to degrading nucleic acids present, and numbered paragraphs 2-4), and page 6, step 4 (for reference to DNase activity). Therefore, no new matter is introduced. The Office Action is discussed below:

Withdrawal of Anticipation and Obviousness Rejections:

In view of the response filed on September 4, 2009, the examiner has withdrawn the rejection of:

- claims 1 and 14 under 35 U.S.C. 102(b) alleged as being anticipated by Bhattacharjee *et al.* US Patent No. 5,919,617 (July 16, 1999);
- claims 1-6 and 14 under 35 U.S.C. 103(a) alleged as being unpatentable over Bhattacharjee *et al.* US Patent No. 5,919,617 (July 16, 1999) in view of Bhattacharjee *et al.* US Application No. 20030039981 (February 27, 2003, Filing Date November 27, 2001), and Switchenko *et al.* US Patent No. 5,563,038 (October 8, 1996);
- claims 1, 10-12, and 14 under 35 U.S.C. 103(a) alleged as being unpatentable over Bhattacharjee *et al.* US Patent No. 5,919,617 (July 16, 1999) in view of Sheiness *et al.* US Patent No. 5,776,694 (July 7, 1998), and Harada *et al.* US Patent No. 4,251,643 (March 16, 1979); and
- claims 1 and 14-17 under 35 U.S.C. 103(a) alleged as being unpatentable over Sheiness *et al.* US Patent No. 5,776,694 (July 7, 1998) in view of Bhattacharjee *et al.* US Patent No. 5,919,617 (July 16, 1999).

Applicants thank the examiner for withdrawal of the Anticipation and Obviousness rejections of the claims.

Written Description Rejection:

On pages 3-6 of the Office Action, the examiner has maintained the rejection of claims 1-6, 10-12, 14-17 under 35 U.S.C. 112, first paragraph, allegedly as failing to comply with the written description requirement.

The Examiner alleges that the claims encompass a vast genus of agents capable of reducing direct inhibition of antibody-antigen interaction by components of the sample, or with the ability of reducing the viscosity of the sample. The Examiner alleges that the specification is silent with regard to what structure (composition) engenders the recited functions in any diagnostic immunoassay method as claimed, and asserts that applicants must adequately describe the agents capable of reducing direct inhibition of antibody-antigen interaction by components of the sample or the ability of reducing the viscosity of the sample.

The Examiner concedes that the specification discloses a variety of different suitable agents for reducing the inhibitory effects of the sample on the diagnostic immunoassay method at pages 5-6 of the specification, including DNase, oxidizing agents, non-ionic alkyl glucosides, polyvinyl alcohol, and polyvinyl pyrrolidine. However, the Examiner alleges that the specification only discloses the efficacy of using DNase and hydrogen peroxide in optimizing samples for use in a dipstick based test. The Examiner asserts that the claims are silent with regard to what agents are capable of the recited function in any diagnostic immunoassay method. The Examiner also alleges that the specification does not specifically state which agents in the limited number of species disclosed correlate to the recited functions. The Examiner asserts that absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of inhibitory effects, the

skilled artisan could not immediately recognize or distinguish members of the claimed genus.

Without acquiescing to the Examiner's rejection, applicants amend claim 1 to recite that the agent reduces direct inhibition of antibody-antigen interaction by components of the sample by one or more selected from the group consisting of: (i) neutralizing components of the sample that physically block antibody-antigen interaction, (ii) neutralizing components which sequester the antigen or which modify charges on the antibody adversely affecting its affinity for the antigen, (iii) reducing inhibition of antibody-antigen interaction by making antigen available for antibody detection, and (iv) reducing viscosity of the sample by degrading nucleic acids present in the sample.

Applicants respectfully disagree with the examiner and submit that the specification is not silent with regard to what structure engenders the recited functions in any diagnostic immunoassay method as claimed. The present invention relates to a method for preparing an endocervical fluid sample or a vaginal fluid sample obtained from a human patient for performing a diagnostic immunoassay. It is explained in the application that such samples are inhibitory to antibody-based tests because the sample contains components that directly inhibit antibody-antigen interaction and that indirectly inhibit the test by preventing proper mixing of reagents and the reduction or inhibition of liquid flow. Methods of the invention overcome these problems to provide treated samples in which antigen present in the samples is better able to interact with antibody specific for the antigen. Since diagnostic immunoassays rely on such interactions, methods of the invention are applicable to any suitable diagnostic immunoassay.

Besides DNase and hydrogen peroxide, the specification discloses the efficacy of using n-dodecyl maltoside as a surfactant, and PVA. It is explained at page 5 of the specification that Table 1 shows that when vaginal swabs were taken from different individuals, spiked with *Chlamydia* elementary bodies, the detection signal is improved in the presence of surfactants, with n-dodecyl maltoside giving the best results. Table 2 shows that when vaginal swabs were taken from different individuals,

spiked with *Chlamydia* elementary bodies, and tested with or without PVA in the extraction solution, the detection signals were stronger in those extracted in the presence of PVA.

Amended claim 1 is not silent with regard to what agents are capable of the recited function in any diagnostic immunoassay method. Amended claim 1 explicitly states that the agent reduces direct inhibition of antibody-antigen interaction by components of the sample by one or more selected from the group consisting of: (i) neutralizing components of the sample that physically block antibody-antigen interaction, (ii) neutralizing components which sequester the antigen or which modify charges on the antibody adversely affecting its affinity for the antigen, (iii) reducing inhibition of antibody-antigen interaction by making antigen available for antibody detection, and (iv) reducing viscosity of the sample by degrading nucleic acids present in the sample.

The skilled person could readily identify from the teaching in the specification which of the disclosed agents have the recited function. Page 4 explains that there are at least two aspects to the inhibitory phenomenon observed with vaginal swab specimens: direct inhibition of antibody-antigen interaction; and indirect inhibition of the test by preventing proper mixing of reagents and the reduction or inhibition of liquid flow. The reasons for these inhibitory effects are explained in detail on page 4. In particular, direct inhibition of the interaction between antibodies and their target antigen may be through physically blocking the antibody and antigen from coming together, sequestration of the antigen target, or modification of charges on the antibody molecule adversely affecting its affinity. Inhibition of proper mixing and liquid flow is explained to be related to the inherent viscosity of vaginal fluid, two of the main contributors being mucin levels and amounts of DNA in the sample. Suitable agents for reducing the inhibitory effect of the sample, and their mechanism of action, are described at pages 4-5 of the specification. In particular, it is explained at page 5 that nucleic acids present in the sample can be degraded by DNase, inhibitory substances in the sample can be neutralized by oxidation with oxidizing agents such as hydrogen peroxide, and that antigen is made available for antibody detection by use of

surfactants, such as n-dodecyl maltoside, which extract antigen from the sample, or PVA or PVP which act as an antigen carrier or enhance the formation of antigen micelles.

The specification does, therefore, describe the agents capable of reducing direct inhibition of antibody-antigen interaction by components of the sample and the ability of reducing the viscosity of the sample, and specifically states which agents correlate to the recited functions, and the skilled artisan can immediately recognize and distinguish members of the claimed genus.

In view of the above, applicants request withdrawal of the written description rejection.

Enablement Rejection:

On pages 6-10 of the Office Action, the examiner has maintained the rejection of claims 1-6, 10-12 and 14-17 under 35 U.S.C. 112, first paragraph, allegedly as being non-enabling.

The Examiner concedes that the claims are enabled for a method for preparing an endocervical or vaginal fluid sample obtained from a human patient for performing a dipstick based diagnostic method to detect whether the patient has been infected with *Chlamydia trachomatis* utilizing DNase, but alleges that the claims are not enabled across their full breadth. The Examiner asserts that the claims encompass any agent for reducing an inhibitory effect of the sample, reducing direct inhibition of antibody-antigen interaction by components of the sample, and reducing the viscosity of the sample. The Examiner alleges that the data in the application does not demonstrate that any agent as claimed can perform the recited functions.

Applicants disagree with the examiner and submit that the amended claims do not encompass any agent for reducing an inhibitory effect of the sample, reducing direct inhibition of antibody-antigen interaction by components of the sample, and reducing the viscosity of the sample. Without acquiescing to the Examiner's rejection, Applicants have amended claim 1.

As explained above, besides DNase and hydrogen peroxide, the specification discloses the efficacy of using surfactants, and PVA.

The examples relate to detection of *Chlaymdia trachomatis*. However, it is clear to the skilled person from the teaching in the specification that treatment of samples with the specified agents will improve detection of other infectious agents because the agents used to treat the sample are not limited in their effects specifically to *Chlamydia* antigen. In particular, the agents neutralize components of the sample that physically block antibody-antigen interactions or which sequester antigen or which modify charges on antibody molecules adversely affecting their affinity for antigen, or reduce inhibition of antibody-antigen interactions by making antigen available for antibody detection, or reduce viscosity of the sample by degrading nucleic acid present in the sample. The recited agents have a more general effect on the quality of the sample, thereby improving interaction of antibodies with target antigen in general.

Accordingly, withdrawal of the enablement rejection is solicited.

New Grounds of Rejections:

Indefiniteness Rejection:

On pages 10-11 of the Office Action, the examiner rejects claims 1-6, 10-12 and 14-17 under 35 U.S.C. 112, second paragraph, allegedly as being indefinite.

The Examiner alleges that claim 1 recites the limitation "the diagnostic method" and asserts that there is insufficient antecedent basis for this limitation in the claims. Without acquiescing to the Examiner's rejection, applicants amend the claim to recite "the diagnostic immunoassay method".

Accordingly, withdrawal of the indefiniteness rejection is requested.

Obviousness Rejections:

On pages 12-14 of the Office Action, the examiner rejects claims 1, 4-5 and 14

under 35 U.S.C. 103(a) allegedly as being unpatentable over Cameron *et al.* (US Patent No. 5,844,097), and Bhattacharjee *et al.* (US Patent No. 5,919,617).

The Examiner alleges that Cameron *et al.* teach a method of diagnosing cervical pain by quantifying or detecting the presence of protein for the diagnosis of chronic cervical pain (CCP) by employing immunoassays that are performed directly on a body fluid sample derived from tissue, serum or other body fluids. The Examiner also alleges that Cameron *et al* teach samples treated with DNase and RNase to reduce the viscosity in said samples.

The Examiner concedes that Cameron *et al.* do not teach a method for preparing an endocervical fluid sample or a vaginal fluid sample obtained from a human patient specifically for performing a diagnostic immunoassay method, which comprises the steps of treating specifically the endocervical fluid sample or the vaginal fluid sample with an agent, wherein the human patient sample is obtained as a self collected vaginal swab sample.

However, the Examiner alleges that Bhattacharjee *et al.* teach swabbing from mucocutaneous membranes such as swabs from the vagina, and methods of using antibodies binding to epitopes contained in a biological sample to detect a fungal pathogen. The Examiner considers that given the samples disclosed in Cameron *et al.* and Bhattacharjee *et al.* used in an immunodiagnostic method for detection of an infectious agent are well known in the art, it would be obvious to combine the teachings of Bhattacharjee *et al.* and Cameron *et al.* to arrive at the claimed method.

Applicants disagree with the Examiner's and clarify that Cameron *et al.* disclose treatment of samples with DNase and RNase to reduce viscosity following first stage gel electrophoresis of the sample, and prior to second stage gel electrophoresis, and subsequent transfer of proteins from the gel to a matrix and detection by labeled antibody (see column 10, line 58 – column 13, line 36). However, there is no disclosure in Cameron *et al.* that the immunological test is carried out in the presence of DNase. In particular, there is no disclosure that the DNase is transferred to the matrix and present during the antibody detection step. Even if the diclosure were present, the conditions of second stage gel electrophoresis (carried

out in the presence of SDS and polyacrylamide) would be expected to inactivate the DNase prior to the antibody detection step.

Whilst Bhattacharjee *et al.* describe methods of using antibodies to detect a fungal pathogen in a biological sample, there is no disclosure of performing such assays in the presence of DNase. Consequently, no combination of the cited references can render the claimed subject matter obvious.

Also, there is no disclosure in either Cameron *et al.* or Bhattacharjee *et al.* of the need to treat endocervical or vaginal fluid samples to reduce an inhibitory effect of the sample on a diagnostic immunoassay method, nor any disclosure of how such inhibitory effects may be reduced.

Without acquiescing to the Examiner's rejection, and solely by way of a clarifying amendment, applicants amend claim 1 to recite that the diagnostic immunoassay method is performed in the presence of DNase activity. Withdrawal of the obviousness rejection is therefore solicited.

On pages 14-18 of the Office Action, the Examiner rejects claims 1, 4-6 and 14 under 35 U.S.C. 103(a) allegedly as being unpatentable over Cameron *et al.* (US Patent No. 5,844,097), Bhattacharjee *et al.* (US Patent No. 5,919,617), and Switchenko *et al.* (US Patent No. 5,563,038).

The Examiner raises similar arguments as above with regard to Cameron *et al.*, and Bhattacharjee *et al.* Regarding Switchenko *et al.*, the Examiner alleges that the document teaches a method for detecting antigens in a clinical swab sample, and that antigens can be separated from cellular debris and biological fluids by detergents such as the oxidizing agent hydrogen peroxide, usually in the concentration range of from about 0.01 – 1.0% weight to volume.

The Examiner alleges that it would have been obvious to one of skill in the art to modify the method disclosed by Cameron *et al.* by incorporating hydrogen peroxide for detecting the antigens in a biological sample, as disclosed by Switchenko *et al.*, to remove unwanted cellular debris.

The Examiner appears to consider that hydrogen peroxide is an example of a detergent described by Switchenko *et al.* However, it is clear from the disclosure of Switchenko *et al.* that it is directed to a method for removal of detergents by chemically modifying the detergent to modify or destroy its detergent properties (see column 6, lines 43-45). The detergent includes a modifiable group (see column 5, lines 43-46) which is chemically modified by a modifying agent, such as hydrogen peroxide (see column 6, lines 22-24). Thus, hydrogen peroxide is not a detergent, but a modifying reagent used to destroy a detergent, and so Switchenko *et al.* teach use of oxidizing agents for removal of a detergent added to a sample. There is no disclosure that oxidizing agents may be used to treat the sample itself to reduce an inhibitory effect of the sample on a diagnostic immunoassay method. Also, there is no disclosure in Switchenko *et al.* (or Bhattacharjee *et al.* (US Patent No. 5,919,617) of performing a diagnostic immunoassay method in the presence of DNase. Thus, no combination of the cited references can render the claimed subject matter obvious. Accordingly, withdrawal of the rejection is requested.

On pages 18-21 of the Office Action, the Examiner rejects claims 1-5 and 14 under 35 U.S.C. 103(a) allegedly as being unpatentable over Cameron *et al.* (US Patent No. 5,844,097), Bhattacharjee *et al.* (US Patent No. 5,919,617), and Bhattacharjee *et al.* (US Publication No. 2003/0039981).

The Examiner raises similar arguments as above with regard to Cameron *et al.*, and Bhattacharjee *et al.* (US Patent No. 5,919,617). Regarding Bhattacharjee *et al.* (US Publication no. 2003/0039981), the Examiner alleges that the document teaches a method and materials for detecting a presence of a fungus in a biological sample wherein biological samples may be RNA isolated from mixtures of DNA and RNA by using selective exonucleases, such as DNase (citing paragraph 0038) of US Publication No. 2003/0039981. The Examiner asserts that it would have been obvious to modify the method of Cameron *et al.* by incorporating an amount of DNase disclosed by Bhattacharjee *et al.* (US Publication No. 2003/0039981) in order to take advantage of its ability to increase sensitivity in diagnostic methods.

Paragraph 0038 of Bhattacharjee *et al.* as cited by the Examiner relates to use of DNase for isolation of RNA from mixtures of DNA and RNA for detection of the isolated RNA (or cDNA obtained from the isolated RNA) by nucleic acid hybridization (see paragraphs [0042] and [0043]). Bhattacharjee *et al.* (US Publication No. 2003/0039981) contains no disclosure of performing a diagnostic immunoassay method in the presence of DNase. Also, there is no disclosure in Bhattacharjee *et al.* (US Patent No. 5,919,617) of performing a diagnostic immunoassay method in the presence of DNase. Thus, no combination of the cited references can render the claimed subject matter unpatentable. Withdrawal of the rejection is therefore solicited.

On pages 21-25 of the Office Action, the Examiner rejects claims 1, 4-5, 10-12, and 14 under 35 U.S.C. 103(a) allegedly as being unpatentable over Cameron *et al.* (US Patent No. 5,844,097), Bhattacharjee *et al.* (US Patent No. 5,919,617), Sheiness *et al.* (US Patent No. 5,776,694), and Harada *et al.* (US Patent No. 4,251,643). Applicants respectfully disagree with the Examiner and submit the following in order to assist the Examiner in distinguishing the claimed invention from the cited references or any combination thereof:

With regard to Cameron *et al.* and Bhattacharjee *et al.*, the Examiner raises similar arguments as discussed above. Regarding Sheiness *et al.*, the Examiner alleges that this document teaches a method and kit for selectively detecting a microorganism in vaginal samples associated with vaginal disorders obtained from a human patient, wherein the sample is treated with PVP, comprising a working concentration of 0.02% (w/v).

The Examiner alleges that it would have been obvious at the time the invention was made to modify the method of Cameron *et al.* by incorporating a PVP as disclosed in Sheiness *et al.* in order to take advantage of its ability to absorb water and swell rapidly and generate a swelling force to detect organisms in a sample. The Examiner also alleges that it would have been equally obvious to modify the method disclosed in Cameron *et al.* by incorporating PVA for detecting antigens in a biological

sample as an adhesive by embedding and preserving particles in a sample to detect organisms.

Regarding Harada *et al.*, the Examiner alleges that this document teaches absorbent materials for aqueous fluids, which absorb fluid rapidly and swell uniformly, comprising modified polyvinyl alcohol polymers obtained by reacting in an anhydrous condition a polyvinyl alcohol polymer. The Examiner alleges that Harada *et al.* teach PVA type polymers that may be used as starting materials for making absorbent materials and further teach PVAs with molecular weights of 100-5000 g/mol. The Examiner appears to have cited this document to support the assertion that the amount of PVA specified in claim 11 is the result of routine experimentation.

Sheiness *et al.* relates to methods for releasing nucleic acid from a microorganism. The cited reference to PVP in this document (see column 31, lines 24-29) relates to inclusion of PVP in a hybridization/slot blot solution. Use of this solution is described in Example 6 for hybridization of a labeled oligonucleotide with filters fixed with released RNA (column 40, lines 7-15). There is no disclosure of treatment of an endocervical fluid sample or a vaginal fluid sample with PVP. Also, there is no disclosure of diagnostic immunoassay methods in this document.

Regarding Harada *et al.*, the Examiner alleges that it would have been obvious to one of skill in the art to modify the method of Bhattacharjee *et al.* by incorporating PVA for detecting the antigens in a biological sample (as disclosed by Sheiness *et al.*) as an adhesive by embedding and preserving particles in a sample to detect organisms. The Examiner's citation of this document is perplexing. It appears to have been cited simply because it contains the term "polyvinyl alcohol", without any consideration by the Examiner as to the teaching of this document. The Examiner does not point to any teaching in Harada *et al.* that would have led the skilled person to use PVA as an adhesive to embed and preserve particles, and the Examiner makes no suggestion as to how this would reduce an inhibitory effect of the sample on the diagnostic method. There is no teaching in Harada *et al.* that treatment of endocervical fluid samples or vaginal fluid samples with PVA could reduce the inhibitory effect of the sample on a diagnostic immunoassay. Indeed, use of the

absorbent materials described by Harada *et al.* in a method of the invention would be expected to severely inhibit an immunoassay, since they would absorb water from the sample, thereby inhibiting the immune reaction.

Since neither Sheiness *et al.* nor Bhattacharjee *et al.* (US Patent No. 5,919,617) nor Harada *et al.* disclose performing diagnostic immunoassay methods in the presence of DNase, and there is no disclosure in any of these documents of treatment of an endocervical fluid sample or a vaginal fluid sample with PVP or PVA, no combination of the cited references can render the claimed subject matter obvious. Accordingly, withdrawal of the rejection is solicited.

On pages 25-28 of the Office Action, the Examiner rejects claims 1, 4-5, and 14-17 under 35 U.S.C. 103(a) allegedly as being unpatentable over Sheiness *et al.* (US Patent No. 5,776,694) and Cameron *et al.* (US Patent No. 5,844,097).

The Examiner alleges that Sheiness *et al.* teach a method and kit for selectively detecting *Chlamydia* in vaginal samples associated with vaginal disorders obtained from a human patient. The Examiner concedes that Sheiness *et al.* does not teach a method comprising the steps of specifically treating a sample with an agent to reduce an inhibitory effect of the sample on the diagnostic method, wherein the agent reduces direct inhibition of antibody-antigen interaction by components of the sample or wherein the agent reduces viscosity of the sample, and specifically performing a diagnostic immunoassay method in the presence of DNase. However, the Examiner alleges that it would have been obvious at the time the invention was made to modify the method of Sheiness *et al.* by incorporating a DNase as disclosed by Cameron *et al.* in order to take advantage of preserving samples from a patient with cervical pain.

Again, applicants disagree with the Examiner and point out that Cameron *et al.* disclose treatment of samples with DNase and RNase to reduce viscosity following first stage gel electrophoresis of the sample, and prior to second stage gel electrophoresis, and subsequent transfer of proteins from the gel to a matrix and

detection by labeled antibody (see column 10, line 58 – column 13, line 36). However, there is no disclosure that the immunological test is carried out in the presence of DNase. In particular, there is no disclosure that the DNase is transferred to the matrix and present during the antibody detection step. Even if it were present, the conditions of second stage gel electrophoresis (carried out in the presence of SDS and polyacrylamide) would be expected to inactivate the DNase prior to the antibody detection step.

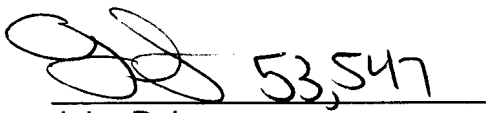
Thus, there is no disclosure in Sheiness *et al.* or Cameron *et al.* of performing a diagnostic immunoassay in the presence of DNase. Consequently, no combination of the cited references can render the claimed subject matter unpatentable. There is also no disclosure in either Sheiness *et al.* or Cameron *et al.* of the need to treat endocervical or vaginal fluid samples to reduce an inhibitory effect of the sample on a diagnostic immunoassay method, nor any disclosure of how such inhibitory effects may be reduced.

In view of the above clarifications and amendment to claim 1, applicants request withdrawal of the obviousness rejections.

REQUEST

Applicants submit that claims 1-6, 10-12, and 14-17 are in condition for allowance and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 416-6800 should there be any questions.

Respectfully submitted,



April 16, 2010
Date

John P. Isacson
Reg. No. 33,715

PERKINS COIE LLP
607 Fourteenth Street, NW
Washington, D.C. 20005-2003
Phone: 202.628.6600
Fax: 202.434.1690
Customer No. 61263